RESPONSE

Pending claims

Claims 24, 26, and 28-32 are pending and presented for examination. The amendments to the specification are made to respond to the Examiner's objections and to correct informalities. They introduce no new matter.

The present invention is drawn to a method of screening a helminthic parasite preparation for one or more components that reduce an excessive Th1 immune response. Excessive Th1 responses are associated with a number of pathological conditions such as inflammatory bowel disease, rheumatoid arthritis, Crohn's disease and ulcerative colitis. The invention relates to identifying components in a helminthic preparation that will reduce an excessive Th1 response by inducing a Th2 response.

Objection to the Specification

The Examiner has objected to the Application for containing a sequence which fails to comply with the requirements of 37 § 1,821 through 1.825 but has not supplied Applicants with a Notice To Comply With Requirements For Patent Applications Containing Nucleotide And/Or Amino Acid Sequence Disclosure. As discussed above, Applicants have provided herewith a paper copy sequence listing and CRF, but necessarily have not included a Copy of the Notice to Comply. Applicants thank the Examiner for calling their attention to this matter, and respectfully submit that in view of their Response, the objection should be reconsidered and withdrawn.

The Examiner has also objected to the amendment of September 12, 2001 which deleted IgG2a from page 22, line 14 and replaced it with IgG2, but inadvertently failed to delete the last occurrence of IgG2. Applicants submit herewith a replacement specification page to correct this error and a marked-up version of the specification to show where changes have been made. Applicants additionally submit replacement specification page 49 to indicate the sequence on this

page by its appropriate SEQ ID NO. Applicants respectfully submit that in view of this response the objection should be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 24, 26, and 28-32 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that the specification does not reasonably provide enablement for a method of screening an helminthic parasite preparation for one or more components that reduce excessive Th1 immune responses, the preparation prepared by fractionating and sub-fractionating the helminthic preparation. The Examiner states that there is no guidance in the specification as to how one would obtain sub-fractions of the homogenate and which subfractions would possess the claimed functions.

Applicants respectfully traverse the rejection. Applicants provide detailed teachings at pages 20 through 31 as to how to obtain fractions and subfractions of helminthic homogenates. Further, such techniques are well known in the art. It is in fact unclear what basis the Examiner has to support the conclusion that the specification does not reasonably teach how to perform the various steps of homogenating, fractionating and subfractionating, when the Examiner herself has acknowledged that such methods are routine in the art (see, e.g., Office Action at page 6, for example). Further, Applicants provide detailed teachings in the specification of assays to evaluate which fractions and subfractions of an helminthic homogenate possess the requisite biological activity of reducing an excessive Th1 both *in vitro* and *in vivo*. For example, assays to measure *in vivo* responses are described at the last paragraph of page 21 through the bridging paragraph of page 22 (e.g., assays which measure cytokine and immunoglobulin profiles and assays to measure Fcg3 and MHC Class II molecules), at page 31, first full paragraph page 31 (which describes animal models which can be used) and pages 24-39 (which describes assays for measuring inflammation as a means of evaluating Th1 responses in both animals and humans). *In vitro* assays are described at page 23, second paragraph, and pages 31-32. Methods of measuring cytokines and immunoglobulins also are described at pages 22-23 as a means of

evaluating reduction in Th1 responses and/or induction of Th2 responses. The Examiner herself has also stated that *in vitro* or *in vivo* assays are simply a matter of design choice; again acknowledging that the assays themselves are routine.

Further, Applicants do not understand the Examiner's seeming requirement that Applicants describe the molecular weights of components obtained from the fractions and subfractions being identified using the claimed method and to identify "which sub-fractions would possess the claimed functions" (Office Action, page 3, second full paragraph). The end result of the method is to *identify* components of helminthic homogenates which reduce an excessive Th1 responses; therefore *a priori* the molecular weights of such compounds cannot be known by Applicants nor can Applicants specifically point to particular fractions which possess the activity. The claimed methods are not drawn to purifying *known* components but to identifying *unknown* components of helminthic homogenates to produce therapeutic reagents for reducing an excessive Th1 response.

Moreover, at page 4 of the Office Action, the Examiner has mischaracterized the assay that was performed on page 38 of the instant specification to demonstrate that homogenates themselves have activity. Mycobacterial antigens were not necessary to *reduce* an excessive Th1 response, they were used to *enhance* a Th1 response in order to create a model in which the effects of the homogenate in reducing the response could be measured (see, as described on page 30, last paragraph). There was no showing of fractionation or subfractionation in the Examples because the Examples do not relate to the screening assay being claimed but instead demonstrate the effectiveness of helminthic homogenates themselves in reducing a Th1 response. The Examiner appears to be requiring working examples demonstrating specific components identified from helminthic homogenates which reduce Th1 responses without having met the burden of showing that the teachings of the specification, in light of what was known in the art, would not identify such components by performing the method as claimed. Again, it is unclear how the Examiner can state that methods of identifying fractions and subfractions with a particular biological activity are routine in the art under 35 U.S.C. § 103(a) yet not enabled under

35 U.S.C. § 112 first paragraph. Accordingly, Applicant respectfully submits the rejection under 35 U.S.C. § 112 is improper, and respectfully requests that the rejection be reconsidered and withdrawn.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 26 and 32 under 35 U.S.C. § 112, second paragraph, asserting that the claims are indefinite because it is unclear in claim 26, where the further steps are to be performed, after separating the fractions or after assaying the fractions. The Examiner also states that claim 32 is unclear with respect as to how one would assay activity *in vivo*.

Applicants respectfully traverse the rejections. Claim 26 encompasses either scenario suggested by the examiner; the step of further fractionating and assaying can be performed after *either* after a fractionating step or an assaying step-there is nothing ambiguous about the claim. The metes and bounds of claim 36 are equally clear; the claim encompasses any assay which is performed *in vivo* to detect a reduction in an excessive Th1 immune response; if an assay is performed *in vivo* and provides a measure of a Th1 response, it falls within the scope of the claims. The Examiner is respectfully reminded that breadth of a claim is not to be equated with indefiniteness. See *In re Miller*, 441 F.2d 689, 169 U.S.P.Q. 597 (CCPA 1971). Accordingly, Applicants respectfully submit because the meaning of every term in the claims would be clear to those of ordinary skill in the art, the rejection under 35 U.S.C. § 112 is improper and should be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 24, 26, 28-32 under 35 U.S.C. § 103(a) as being obvious in view of Metwali et al., 1996 ("Metwali") and Boros et al., 1970 ("Boros"). The Examiner asserts that Metwali teaches a method of determining the role of IL-4 in regulating the production of IFN-γ and Th1 inflammation in the granulomas from mice infected with *Schistosoma mansoni* by assaying for the production of cytokines before and after stimulation

with a soluble egg antigen prepared from schistosome eggs. The Examiner asserts that Metwali's teachings "suggest that there are substances or components in [*S. mansoni*] eggs which reduce Th1 (i.e., IFN-γ activity)." The Examiner acknowledges that Metwali does not specifically describe fractionating the antigen and subjecting the antigen to chromatographic techniques. However, the Examiner asserts that Boros remedies this deficiency in teaching a method of isolating antigens from *S. mansoni eggs*. The Examiner states that the criticality of an *in vitro* or *in vivo* assay has not been established and would be a manner of design choice.

Claims 24, 26, and 28-32 also are rejected under 35 U.S.C. § 103(a) as obvious over Pearce et al., 1991 ("Pearce 1991"), in view of Pearce et al., 1988 ("Pearce 1988"). The Examiner states that Pearce 1991 teaches a method of identifying antigens from the helminthic parasite *S. mansoni* which reduce Th1 immune responses. The Examiner acknowledges that Pearce 1991 differs from the claimed invention by not teaching homogenizing, separating homogenate fractions and identifying sub-fractions of helminthic preparations for biological activity, but asserts that Pearce 1988 remedies this deficiency by teaching such methods. The Examiner asserts that "it would have been expected, barring evidence to the contrary, that the purified shistosoma antigens would be identified for their capability of reducing excessive Th1 responses because Pearce 1991 specifically identify and compare antigens and their abilities to down regulate Th1 production." The Examiner again asserts that the criticality of an *in vitro* or *in vivo* assay has not been established and would be a matter of design choice.

Metwali does not describe assays in which effects on an *excessive* Th1 response are monitored. Metwali teaches injection of schistosomes into normal mice or mice which are IL-4-/IL-4-. As discussed in the Metwali article, at page 4552, column 1, first full paragraph, IL-4- is not the sole mediator of a Th1 response and so knocking out IL-4 does not necessarily create an excessive Th1 response. In fact IL-4-/IL-4- mice *do* stimulate IFN- γ expression upon stimulation with SEA (page 4552, column 1, bridging paragraph) suggesting that these animals *do not* model an excessive Th1 response. Further, these animals are not able to mount a proper Th2 response (see page 4546, column 2, last paragraph). Thus, one of skill in the art at the time

that the invention was made *would be led away* from using the test system of Metwali to determine which portions of a helminthic preparation would decrease a Th1 response as one would not be motivated to use an animal with a deficient Th2 response to screen for components which decrease a Th1 response nor would the skilled artisan be motivated to use a normal mouse to model a disease state. Finally, Metwali provides reasons *not* to fractionate or subfractionate schistosome preparations by suggesting that it is *attachment* of schistosome ova to the intestinal wall and lumen of animals that causes the modulation of systemic inflammation (page 4552, column 1 last paragraph). Therefore, one of skill in the art would not expect that fractions or subfractions of a helminthic preparation would have a therapeutic effect as such preparations *would not mimic a natural infection.*

Similarly, Pearce 1991 does not actually teach that helminthic preparations of any sort reduce an *excessive* Th1 response. Pearce 1991 injects his helminthic preparations into *normal* C57BL/6 mice and merely reports the effect of helminthic preparations on *normal Th1* responses. Pearce provides no teaching or suggestion to modify his method to obtain fractions or subfractions of a helminthic preparation to reduce an *excessive* Th1 response (e.g., such as a chronic inflammatory immune disease) and therefore, although one might know from the teachings of Pearce 1989 how to obtain fractions and subfractions in general, one would not know what assays to use to identify fractions of particular interest, i.e., fractions or subfractions which reduce an excessive Th1 response.

Accordingly, Applicants respectfully request that in view of the above arguments, the Examiner reconsider and withdraw the rejections of the claims.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially

invited to call the undersigned attorney of record.

Respectfully submitted,

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